

## AMENDMENTS TO THE CLAIMS

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FEB 17 2009

1. [Cancelled]
2. [Cancelled]
3. [Cancelled]
4. [Currently Amended] A method for determining the genetic affinity of organisms or viruses in a test sample containing a nucleic acid comprising in combination the steps of:
  - A. Obtaining or creating a nucleic acid database of the same target nucleic acid sequences of a homologous target RNA or DNA, from all organisms or viruses that will be incorporated into the determination analysis;
  - B. Obtaining or developing a bifurcating ~~node~~ phylogenetic tree having multiple nodes that establishes the genetic affinity that reflects the genetic relationship between the organisms or viruses included in a the nucleic acid database of sequences of the target nucleic acid;
  - C. Computationally fragmenting each target nucleic acid sequence so as to create a subsequence database of nucleic acid subsequences of length N that occur in at least two sequences in the nucleic acid database, where N is at least seven;
  - C. ~~Identifying the extent to which the presence of each particular oligonucleotide RNA or DNA subsequence of length N is charastie of each node in the bifurcating phylogenetic tree of genetic relationship by examining the occurrence frequency of each subsequence in the target nucleic acid of the organisms and viruses encompassed by or not encompassed by each node in the tree;~~

~~D. Identifying~~ Creating a signature database by tabulating the extent to which the presence of each particular RNA or DNA nucleic acid subsequence of length N in the subsequence database is characteristic of each node in the bifurcating phylogenetic tree of genetic relationship by examining the occurrence frequency of each subsequence in the target nucleic acids acid of the organisms and viruses encompassed by or not encompassed by each node in the tree.;

~~D. Maintaining or creating as needed, a signature database that tabulates the extent to which each subsequence of length N in the subsequence database is a characteristic signature of each individual node in the bifurcating phylogenetic tree;~~

~~E. Deriving a plurality of signature probes from a the signature database of characteristic signature sequences that will be are complementary to a portion of the target nucleic acid sequence of the organism or virus if the signature sequence is present, such that the number of organisms or viruses whose genetic affinity can might be determined is at least twice the number of probes used;~~

~~F. Hybridizing the signature probes to the target nucleic acid obtained from the test sample under conditions where a detectable signal will be produced by signature probes that hybridize to the target nucleic acid of the organism or virus and detecting such signals;~~

~~G. F. Identifying signature probes which produce detectable signal;~~

~~F. Using the characteristic signature database of characteristic signature sequences to determine~~ Identifying the nodes in the bifurcating phylogenetic

tree of genetic relationship that are represented by the signature probes that produced detectable signal, in order to ~~identify~~ determine the closest genetic affinity ~~relatives~~ of the organism or virus in the test sample.

5. [Currently Amended] A method of claim 4 wherein the signature probes ~~are comprised of~~ comprise a moiety selected from the group consisting of: RNA, DNA, an analog of RNA or DNA including peptide nucleic acids, 2'-O-methyl DNA or any other molecule that can interact with the test sample nucleic acid in a sequence-specific way.

6. [Previously Presented] A method of claim 4 wherein the hybridization step utilizes a feature selected from the group consisting of an immobilized array of signature probes, molecular beacons and a hybridization step done in solution.

7. [Previously Presented] A method of claim 4 wherein the detection step utilizes radioactive labels, chemiluminescence and/or fluorescence.

8. [Previously Presented] A method of claim 4 wherein the bifurcating ~~node~~ phylogenetic tree of genetic relationships is generated by parsimony method.

9. [Previously Presented] A method of claim 4 wherein the most narrowly defined grouping on the tree of relationship comprises a moiety selected from the group consisting of: a specific genus, a specific species, a race, serotype, type ~~or~~ and another ~~other~~ grouping below the species level.

10. [Currently Amended] A method of claim 4 in which the extent to which each particular oligonucleotide or sequence of length N is characteristic of each node in the tree of genetic relationship is identified by:

A. Compiling a database of at least 12 target nucleic acid sequences from a ~~substantially homologous RNA or DNA comprising sequences~~ all organisms or viruses that will be incorporated into the analysis;

B. Calculating the occurrence frequency and distribution of ~~oligoribonucleotide or oligodeoxyribonucleotide~~ sequences each subsequence of length N in the sequence data base;

C. Calculating a signature quality function which measures the extent to which each subsequence ~~particular oligoribonucleotide or oligodeoxyribonucleotide~~ sequence of length N is characteristic of each node in the bifurcating node phylogenetic tree of genetic relationships.

11. [Cancelled]

12. [Cancelled]

13. [Cancelled]

14. [Cancelled]

15. [Cancelled]

16. [Cancelled]

17. [Cancelled]

18. [Cancelled]

19. [Currently Amended] A method of Claim 4 in which the signature probes are of length 6 or larger and where the nucleic acid is selected from the group consisting of ribosomal RNA, genomic DNA, 10S RNA, RNase P RNA, guide RNA, telomerase RNA, snRNAs, scRNAs, and DNA isolated from the spacer region between ribosomal RNA genes ~~or a fragment and~~ fragments of the foregoing.

20. [Cancelled]

21. [Previously Presented] A method of claim 4 wherein the hybridization step comprises a feature selected from the group consisting of locked nucleic acids, polymerase chain reaction, RT-PCR, peptide nucleic acids, array detection, and magnetic detection.

Claim 22 [Cancelled]

23. [Currently Amended] A method of claim 10 in which the signature quality index,  $Q_s$ , is calculated by substantially the equation:

$$\begin{aligned} Q_s &= (N_{GM} / N_{GT}) \times (1 - (N_M - N_{GM}) / N_M) \\ &= (N_{GM}^2) / (N_{GT} \times N_M) \end{aligned}$$

in which  $N_M$  is the number of probe-matched organisms in the entire tree,  $N_{GM}$  is the number of probe-matched organisms in the group of interest, and  $N_{GT}$  is the number of organisms in the group under consideration.

24. [Previously Presented] A method of claim 4 in which the oligonucleotides or sequences of length  $N$  comprise genes.

25. [Cancelled]

26. [Cancelled]

27. [Cancelled]

28. [Previously Presented] A method of Claim 10 in which the signature quality function is calculated by a single formula which includes both the presence of sequences in a particular group of organisms or viruses and their presence in other organisms not belonging to that group of organisms or viruses.

29. [Currently Amended] A method of Claim 4 in which the signature probes used have values of  $Q_s$  averaging less than 0.95 when calculated by substantially the equation:

$$\begin{aligned} Q_s &= (N_{GM} / N_{GI}) \times (1 - (N_M - N_{GM}) / N_M) \\ &= (N_{GM}^2) / (N_{GI} \times N_M) \end{aligned}$$

in which  $N_M$  is the number of probe-matched organisms in the entire tree,  $N_{GM}$  is the number of probe-matched organisms in the group of interest, and  $N_{GI}$  is the number of organisms in the group under consideration.

30. [Cancelled]

31. [Cancelled]

32. [Cancelled]

33. [Cancelled]

34. [Cancelled]

35. [Cancelled]

36. [Cancelled]

37. [Cancelled]

38. [Cancelled]

39. [New] A method of claim 4 wherein the tree comprises 11 or more nodes.

40. [New] In a method for determining the genetic affinity of organisms or viruses in a test sample containing a nucleic acid under conditions where a detectable signal is produced by signature probes that are hybridized to the target nucleic acid of the organism or virus and detecting such signals and identifying the nodes in a multiple node bifurcating phylogenetic tree of genetic relationship that are represented by the signature probes that produced such signals;

the improvement comprising in combination:

A. Obtaining or creating a nucleic acid database of target nucleic acid sequences of a homologous target RNA or DNA, from all organisms or viruses that will be incorporated into the determination;

B. Obtaining or developing a bifurcating node phylogenetic tree having multiple nodes that establishes the genetic affinity of the organisms or viruses included in a the nucleic acid database of sequences of target nucleic acid;

C. Computationally fragmenting each target nucleic acid sequence so as to create a subsequence database of nucleic acid subsequences of length N that occur in at least two sequences in the nucleic acid database;

D. Maintaining or creating as needed, a signature database that tabulates the extent to which each subsequence of length N in the subsequence database is a characteristic signature of each individual node in the bifurcating phylogenetic tree; and

E. Deriving a plurality of signature probes from the signature database that will be complementary to a portion of the target nucleic acid sequence of the organism or virus if the signature sequence is present.

41. [New] A method of claim 4 wherein the target nucleic acid comprises RNA or DNA.

42. [New] A method of claim 4 comprising selecting a target nucleic acid from the group consisting of: ribosomal RNAs, RNase P RNA, tmRNA, and the DNA that encodes them, spacer region DNA from rRNA gene clusters, mitochondrial DNA, and viral genomic RNAs and DNAs.

43. [New] A method of Claim 40 wherein a target nucleic acid is selected from the group consisting of: ribosomal RNAs, RNase P RNA, tmRNA, and the DNA that encodes them, spacer region DNA from rRNA gene clusters, mitochondrial DNA, and viral genomic RNAs and DNAs.

43. [New] A method of claim 4 comprising inspecting the location of positive nodes in the phylogenetic bifurcating tree to determine the genetic affinity of the organism or virus in the test sample.

44. [New] A method of claim 4 where the same target nucleic acid sequence is obtained from at least 12 organisms or viruses

45. [New] A method according to Claim 40 wherein the tree comprises eleven or more nodes, N equals 7 or more and the nucleic acid database comprises 12 or more sequences.



46. [New] Method of claim 4 in which the nucleic acid database is comprised of at least 12 sequences of a target RNA or DNA, the sequences being derived from different organisms or viruses and being at least 50% identical over at least one subsequence of at least 50 nucleotides.